Evidence-based Practice Center Systematic Review Protocol

Project Title: Chronic Urinary Retention (CUR) Treatment

I. Background and Objectives for the Systematic Review

Chronic Urinary Retention

Urinary retention is the inability to completely empty the bladder of urine.[1] Retention can be complete or partial; acute or chronic. The International Continence Society defined the chronic retention of urine as a nonpainful bladder that remains palpable after voiding.[2] In research settings, chronic urinary retention (CUR) typically describes a persistent inability to completely empty the bladder despite maintaining an ability to urinate, resulting in elevated post-void residual (PVR) urine volumes. There appears to be little standardization in the duration or PVR volume necessary for CUR diagnosis and treatment. Research studies often use PVR volume greater than 300 ml to diagnose CUR; others have used 100 ml, 400 ml, and 500 ml.[1]

The incidence and prevalence of CUR is unknown. Studies of populations of individuals with conditions commonly associated with CUR provide little information regarding the overall burden of CUR. However, it is well-understood that this condition affects elderly men more than any other population.

CUR generally develops slowly over months to years and is not typically painful. CUR may be asymptomatic or may be associated with lower urinary tract symptoms such as urinary frequency, urgency, or incontinence. Causes of retention can be categorized as obstructive, infectious or inflammatory, neurologic, and other.[3] Examples of obstructive causes include benign prostatic hyperplasia (BPH) in men, organ prolapse in women, and urethral strictures in both sexes.[3] Examples of infectious or inflammatory causes include Guillain-Barre syndrome and herpes simplex virus. Examples of neurologic causes include spinal cord injury (SCI), stroke, multiple sclerosis (MS), and diabetes mellitus.[3] Other causes include Fowler's syndrome in women, trauma, postoperative complications and psychogenic.[3]

Patients with CUR may be at increased risk for urinary tract infections (UTI) and experiencing an episode of acute urinary retention (AUR), which is defined as the sudden onset of the complete or near complete inability to urinate despite the urge or effort to do so.[1] AUR typically is associated with lower abdominal pain and may lead to infection, renal failure and/or death.

Testing and Treatment

Treatment for CUR is dependent on etiology. Therefore, providers may first conduct testing to identify the etiology. The presence and severity of symptoms is a consideration in testing decisions. Commonly performed tests include:

- urinalysis (UA)
- urine culture
- measures of renal function
- prostate-specific antigen (PSA)
- urodynamic testing

- renal, bladder, or transrectal prostate ultrasound
- brain or pelvic CT
- brain or lumbosacral spine MRI
- cystoscopy
- retrograde cystourethrography

While testing is commonly performed, there is no standard set of tests or consensus regarding whether testing improves treatment outcomes or induces harms.

Many treatments are available for CUR, including catheterization, surgery, minimally invasive procedures, and pharmacologic treatments. Table 1 lists the various surgical and nonsurgical treatments for CUR. Treatment options available to patients are dependent on etiology. In men it may also be important to determine whether the retention is high-pressure or low-pressure retention (detrusor pressure at the end of micturition) as this may affect treatment decisions.[4] However, there is no consensus regarding the relative benefits and harms of the various options used to treat CUR.

Table 1. Treatments for chronic urinary retention

Intervention	Type or Class
Catheterization	Chronic indwelling catheterization, intermittent catheterization
Surgical interventions (etiology-specific)	Male-specific etiologies: prostate surgeries. Female-specific etiologies: pelvic organ prolapse repair, adjustment to SUI procedures Nonsex-specific etiologies: sacral nerve stimulation Multiple etiologies: urinary diversion procedures
Pharmacological Interventions	Alpha blockers (AB) (doxazosin, prazosin, tamsulosin, terazosin, alfuzosin, silodosin); 5-Alpha Reductase Inhibitors (5-ARI): dutasteride, finasteride; AB + 5-ARI combination therapy: tamsulosin/dutasteride Neurogenic etiologies: botulinum toxin

Decisional Dilemma

The original nomination expressed an interest in a wide range of questions regarding urinary retention (acute and chronic). During the Topic Refinement phase of this project, Key Informants suggested that a review focused on treatment for CUR or incomplete bladder emptying was the highest priority due to the lack of understanding about whether and how to address this condition. Within questions about treatment effectiveness, additional uncertainty, surrounds the clinical relevance of categorizing CUR and the value of using urodynamic testing to direct treatment. Current treatment guidelines do not directly address CUR. Related guidance is available for the treatment for BPH,[5] lower urinary tract symptoms in men,[6] and bladder management in SCI.[7] Results from this CER will inform providers and patients making treatment decisions, organizations developing clinical guidelines, and policymakers making coverage decisions. Results will also describe the limitations of existing evidence and identify research gaps relevant to CUR treatment.

II. The Key Questions

The draft Key Questions developed during AHRQs Topic Refinement process were posted for public comment from October 22, 2012, through November 19, 2012. The comments received suggested that changes to the scope of the draft Key Questions were not necessary. Specifically, comments provided opinions about the status of the evidence and current practice. One comment suggested that two of the interventions listed in our KQ Posting Document are no

longer used in practice. We therefore deleted these interventions from our initial listing. Our revised key questions and PICOTS are below:

KQ1: What is the effectiveness and comparative effectiveness of treatments for chronic urinary retention in adults:

- With male-specific etiologies?
- With female-specific etiologies?
- With nonsex-specific etiologies?

KQ1a: What patient or condition characteristics (e.g., age, severity, etc.) modify the effectiveness of treatment?

KQ2: What are the harms and comparative harms of treatments for chronic urinary retention in adults:

- With male-specific etiologies?
- With female-specific etiologies?
- With nonsex-specific etiologies?

KQ2a: What patient or condition characteristics (e.g., age, severity, etc.) modify the harms of treatment?

The PICOTS (Population, Intervention, Comparison, Outcomes, Timing, and Setting) for all KQs are described in Table 2.

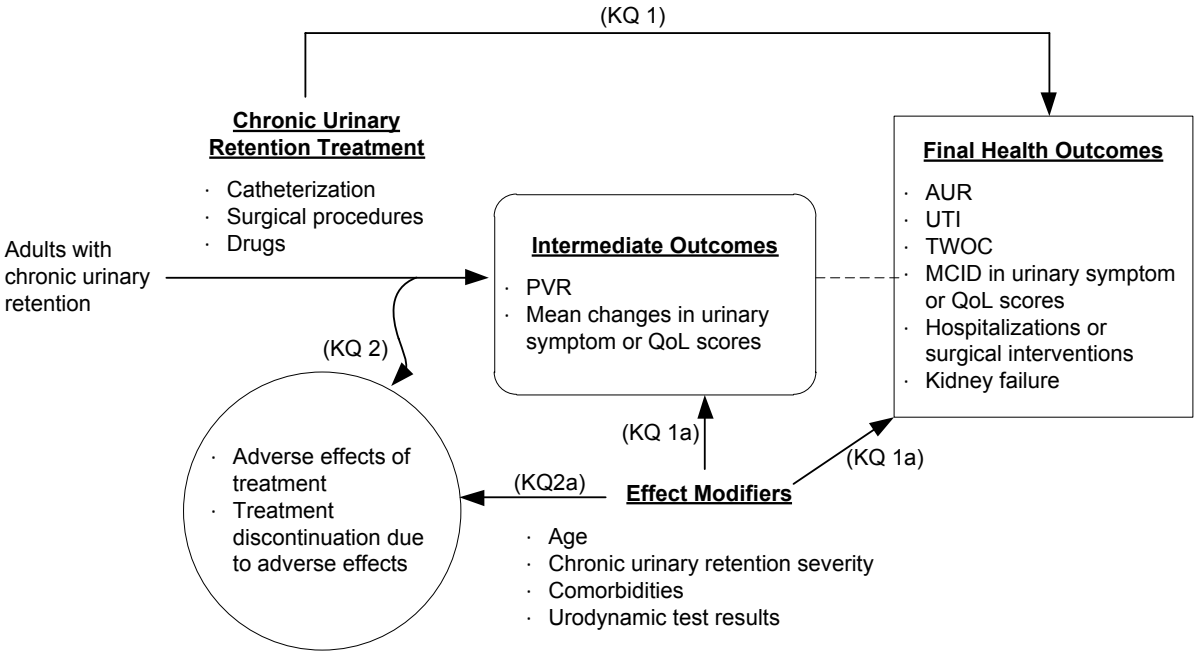
Table 2. PICOTS framework

PICOTS Element	Inclusion Criteria
Population	All adults, 18 or older, with CUR (persistently elevated PVR volume (100 ml or greater) on two measurements – to compensate for measurement error and inconsistency in PVR volumes) except: • CUR attributable to a drug side effect that resolves when drug treatment is stopped or reduced • CUR attributable to a medical or surgical procedure that resolves within short time-frame (postpartum, postoperative due to anesthesia or catheterization) because these cases are considered acute. • CUR attributable to infection/inflammatory etiologies that resolves with antibiotic or antiviral treatment
Intervention	Catheterization Surgical interventions (etiology specific): prostate surgery (BPH); pelvic organ prolapse repair (pelvic organ prolapse); sacral nerve stimulation (neurologic) Pharmacologic treatments: alpha blockers (AB), 5-alpha reductase inhibitors (5-ARI), AB + 5-ARI combination treatment available in the US Urinary diversion
Comparator	Placebo or any of above interventions
Outcomes	Final Health Outcomes: AUR, UTI, catheter outcomes, minimally clinically important change (MCID) in urinary symptom or Quality of Life (QoL) score; need for surgical intervention or hospitalization, kidney failure Intermediate Outcomes: PVR, trial without catheterization (TWOC), urinary symptom or QoL score (mean change)
Timing	Any treatment duration
Setting	Any treatment setting.

III. Analytic Framework

The analytic framework describing the treatment path for adults with CUR appears in Figure 1.

Figure 1. Analytic framework



Abbreviations
AUR – Acute Urinary Retention; MCID – Minimal Clinically Important Difference; PVR – Post Void Residual; QoL – Quality of Life; TWOC – Trial Without Catheterization; UTI – Urinary Tract Infection

Key Questions
KQ1: What is the effectiveness and comparative effectiveness of treatments for chronic urinary retention in adults:
  a. with male-specific etiologies?
  b. with female-specific etiologies?
  c. with nonsex-specific etiologies?
KQ1a: What patient or condition characteristics (e.g., age, severity, etc.) modify the effectiveness of treatment?

KQ2: What are the harms and comparative harms of treatments for chronic urinary retention in adults:
  a. with male-specific etiologies?
  b. with female-specific etiologies?
  c. with nonsex-specific etiologies?
KQ2a: What patient or condition characteristics (e.g., age, severity, etc.) modify the harms of treatment?

V. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review.

Studies will be included or excluded in the review based on the PICOTS framework outlined in Section II and the study-specific inclusion criteria described in Table 3.

Table 3. Study inclusion criteria

Category	Criteria for Inclusion
Study enrollment	Studies that enroll adults with CUR and test the effectiveness of treatments for CUR. AND studies that enroll patients with broader conditions related to CUR (i.e., BPH, Voiding Dysfunction), test treatments that overlap with CUR treatments, provide subgroup analysis of the CUR population IF these studies are registered and subgroup analyses identified a priori in Clinicaltrials.gov
Study Design	Meta-analyses, systematic reviews, RCTs, and nonrandomized controlled trials, will be included for each population and treatment option. Controlled before and after studies may be included for KQs that cannot be answered using trial data alone. The extent of use of previous reviews will be guided by their relevance and quality as determined by investigator assessment.
Time of publication	Search all literature 1946 forward
Study Quality	All studies meeting inclusion criteria will be screened for eligibility. However, studies with a high overall risk of bias will be excluded from full abstraction, synthesis, and SOE assessment. We will qualitatively evaluate the consistency of results of high risk of bias studies with those used in evidence synthesis.
Language of publication	Given that literature on this topic published in English best represents interventions available and accessible in the United States, we will limit inclusion to studies with full text published in English. However, we will not limit our search so that potential language bias can be assessed.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

We will utilize bibliographic database searching to identify previous systematic reviews, randomized controlled trials and observational studies published from 1946 to the present for studies enrolling adults based upon a diagnosis of CUR. Relevant bibliographic databases for this topic include MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL). Our preliminary search strategy appears in Appendix A. This search strategy searches on only one concept, CUR, and employs relevant Medical Subject Headings and natural language terms to find studies on the topic. The concept search is supplemented with filters designed to select experimental designs. Bibliographic database searches will be supplemented with backward citation searches of highly relevant systematic reviews. We will update searches while the draft report is under public/peer review.

Our bibliographic database search and screening process is not designed to find or select studies of broader conditions contributing to CUR in which treatments overlap and subgroup analysis of CUR patients may be reported. A search strategy and screening process for this broad set of conditions is not feasible and the burden likely outweighs potential benefits. The majority of these studies are likely to offer little valuable information given small subgroup sizes and the high risk of selective analysis reporting (subgroup results have been identified in other research as a frequently encountered type of selective analysis reporting).[8]) However, there may be important studies of broader conditions, such as BPH or voiding dysfunction, that specify CUR

subgroup analysis a priori. We will therefore use clinicaltrials.gov to identify studies that specify CUR subgroup analysis in their study protocol.

We will conduct additional grey literature searching to identify relevant completed and ongoing studies. Relevant grey literature resources include trial registries and FDA databases. We will search ClinicalTrials.gov and the International Controlled Trials Registry Platform (ICTRP). We will also review Scientific Information Packets (SIPs) sent by manufacturers of relevant interventions. Grey literature search results will be used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias.

C. Data Abstraction and Data Management.

We will review bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. The use of previous systematic reviews to replace the de novo process will be explored when relevant or partially relevant systematic reviews are identified and judged to be of fair or good quality by using modified AMSTAR criteria.[9] Search dates may be altered in the presence of high quality systematic reviews for specific populations and/or interventions.

Review of bibliographic database searches will occur in two stages. First, titles and abstracts will be reviewed by two independent investigators to identify studies meeting PICOTS framework and study-specific criteria. At this stage we plan to include all interventions identified in the literature. At completion of this stage, we will consult with our TEP to ensure that we capture only studies examining relevant interventions (currently in use in the U.S). All studies identified as relevant by either investigator will undergo full-text screening. Two independent investigators will screen full text to determine if inclusion criteria are met. Differences in screening decisions will be resolved by consultation between investigators and a third investigator if necessary. We will document the inclusion and exclusion status of citations undergoing full-text screening

Studies meeting inclusion criteria will be distributed among investigators for risk of bias assessment and data abstraction. For studies of low to moderate risk of bias, one investigator will abstract relevant study, population demographic, and outcomes data. Data fields to be abstracted will be determined based upon proposed summary analysis. These fields will likely include author; year of publication; setting, subject inclusion and exclusion criteria; intervention and control characteristics (intervention components, timing, frequency, duration); followup duration; participant baseline demographics, comorbidities; CUR definition and method of diagnosis, CUR etiology and severity; descriptions and results of clinical and intermediate outcomes and adverse effects; and study funding source. Relevant data will be extracted into evidence tables. Evidence tables will be reviewed and verified for accuracy by a second investigator.

D. Assessment of Methodological Risk of Bias of Individual Studies.

Risk of bias of eligible studies will be assessed using instruments specific to study design. Existing systematic reviews will be evaluated for quality using a modified AMSTAR criteria.[9] We will assess risk of bias for randomized controlled trials using an instrument we develop based upon the Cochrane Risk of Bias tool.[10] The seven domains included in this tool include sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias (i.e., problems not covered by other domains). Specific study methodology or conduct will be

used to judge potential risk of bias with respect to each domain following guidance in the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0.[10] We will develop an instrument for assessing risk of bias for observational studies using the RTI Observational Studies Risk of Bias and Precision Item Bank.[11] We will select items most relevant in assessing risk of bias for this topic and to foster consistency with the RCT risk-of-bias instrument likely including participant selection; allocation; attempts to balance allocation; effect modifiers and confounders; and appropriateness of analytic methods. We will develop items for both risk-of-bias instruments to assess selective outcome and selective analysis reporting. Investigator assessment of these items will compare reported results to planned analysis described in trial registries and/or the methodology section of the publication as described in a recent AHRQ Methodology report.[8] Overall summary risk of bias assessments for each individual study will be classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results are believable given the study's limitations. Investigators will consult to reconcile any discrepancies in overall risk of bias assessments. When agreement cannot be reached through consultation, a third party will be consulted to reconcile the summary judgment. Studies assessed with an overall high risk of bias will not be included in evidence synthesis due to the low confidence in study results. Information about these studies will be made available in appendices. We will qualitatively compare high risk of bias study results to synthesized evidence as a means of sensitivity analysis. Contradictions will be investigated in further depth.

E. Data Synthesis.

If we find two or more studies for the same comparison, we will consider pooling data from those studies. We will assess the clinical heterogeneity among methodological and PICOTS elements to determine appropriateness of pooling data.[12] When quantitative analysis is not appropriate due to lack of comparable studies or heterogeneity, qualitative synthesis will be conducted.

Study results will be analyzed and synthesized separately for each etiology. In cases where a relevant comparison is adequately addressed by a previous systematic review of acceptable quality, we will use the conclusions drawn from that review unless new data is available to reassess or update the comparison.

F. Grading the Strength of Evidence (SOE) for Individual Comparisons and Outcomes.

The overall strength of evidence for select clinical outcomes (AUR, UTI, TWOC, need for surgical intervention, and clinically minimum difference in urinary symptom or quality of life scale scores) within each comparison will be evaluated based on four required domains: (1) study limitations (internal validity); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate).[13] A fifth domain, reporting bias, will be assessed when SOE based upon the first four domains is moderate or high.[13] Based on study design and conduct, risk of bias will be rated as low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study). Directness will be rated as either direct or indirect. Precision will be rated as precise or imprecise. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders,

and strength of association. Based on these factors, the overall evidence for each outcome will be rated as:[13]

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate:** Moderately confidence that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate and effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

G. Assessing Applicability.

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the specific CUR etiology, narrow eligibility criteria, patient and intervention characteristics different than those described by population studies of chronic urinary retention.[14]

V. References

1. Kaplan SA, Wein AJ, Staskin DR, et al. Urinary retention and post-void residual urine in men: separating truth from tradition. Journal of Urology. 2008 Jul;180(1):47-54. PMID 18485378.
2. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourology & Urodynamics. 2002;21(2):167-78. PMID 11857671.
3. Selius BA, Subedi R. Urinary retention in adults: diagnosis and initial management. American Family Physician. 2008 Mar 1;77(5):643-50. PMID 18350762.
4. Kalejaiye O, Speakman MJ. Management of acute and chronic retention in men. european urology supplements. 2009;8(6):523-9.
5. Nickel JC, Méndez-Probst CE, Whelan TF, et al. 2010 Update: Guidelines for the management of benign prostatic hyperplasia. Canadian Urological Association Journal. 2010;4(5):310.
6. Homma Y, Araki I, Igawa Y, et al. Clinical guideline for male lower urinary tract symptoms. International journal of urology. 2009;16(10):775-90.
7. Linsenmeyer T, Bodner D, Creasey G, et al. Bladder management for adults with spinal cord Injury: A clinical practice guideline for health-care providers. J Spinal Cord Med. 2006;29(5):527-73.
8. Norris S, Holmer H, Ogden L, et al. Selective Outcome Reporting as a Source of Bias in Reviews of Comparative Effectiveness. Agency for Healthcare Research and Quality. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.) Rockville, MD: 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
9. White C, Ip S, McPheeters M, et al. Using existing systematic reviews to replace de novo processes in conducting Comparative Effectiveness Reviews. Agency for Healthcare Research and Quality. Rockville, MD: 2009. http://effectivehealthcare.ahrq.gov/repFiles/methodsguide/systematicreviewsreplacedenovo.pdf.
10. Higgins JPT, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0. The Cochrane Collaboration; 2011.
11. Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. Journal of Clinical Epidemiology. 2011.
12. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of Clinical Epidemiology. 2011 Nov;64(11):1187-97. PMID 21477993.
13. Agency for Healthcare Research and Quality. Grading the strength of a body of evidence when assessing health care interventions--AHRQ and the effective health-care program: An Update Draft Report. Rockville, MD: June 2012. http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1163.
14. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. 2010. http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=603#2412. Accessed on AHRQ Publication No. 11-EHC019-EF.

VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodologic experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present

with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodology expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHSA290-2012-000161from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix A: Search Strategy – MEDLINE

Database: Ovid MEDLINE(R) <1946 to November Week 3 2012> Search Strategy:

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1 exp *Urinary Retention/ (1930)
2 "urinary retention".ti,ab. (5318)
3 "voiding dysfunction".ti,ab. (1312)
4 "incomplete voiding".ti,ab. (50)
5 "voiding difficult*".ti,ab. (423)
6 "underactive bladder".ti,ab. (27)
7 "incomplete bladder empt*".ti,ab. (117)
8 "elevated post void residual".ti,ab. (13)
9 ischuria.ti,ab. (29)
10 or/1-9 (7624)
11 limit 10 to "all child (0 to 18 years)" (1408)
12 limit 11 to "all adult (19 plus years)" (560)
13 1 not 1 (6216)
14 1 or 1 (6776)
15 limit 14 to animals (370)
16 1 not 1 (6406)
17 Randomized Controlled Trials as Topic/ (84921)
18 randomized controlled trial/ (342334)
19 Random Allocation/ (76596)
20 Double Blind Method/ (118498)
21 Single Blind Method/ (17086)
22 clinical trial/ (476450)
23 clinical trial, phase i.pt. (12809)
24 clinical trial, phase ii.pt. (20505)
25 clinical trial, phase iii.pt. (7571)
26 clinical trial, phase iv.pt. (759)
27 controlled clinical trial.pt. (85694)
28 randomized controlled trial.pt. (342334)
29 multicenter study.pt. (153247)
30 clinical trial.pt. (476450)
31 exp Clinical Trials as topic/ (264416)
32 or/17-31 (949526)
33 (clinical adj trial$).tw. (178736)
34 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (116076)
35 PLACEBOS/ (31583)
36 placebo$.tw. (141131)
37 randomly allocated.tw. (14209)
38 (allocated adj2 random$).tw. (16559)
39 3 or 3 or 3 or 3 or 3 or 3 (363492)
40 Epidemiologic studies/ (5579)
41 exp case control studies/ (586243)
42 exp cohort studies/ (1234174)
43 Case control.tw. (63924)
44 (cohort adj (study or studies)).tw. (65854)

45 Cohort analy$.tw. (2895)
46 (Follow up adj (study or studies)).tw. (33920)
47 (observational adj (study or studies)).tw. (33241)
48 Longitudinal.tw. (115334)
49 Retrospective.tw. (223737)
50 Cross sectional.tw. (130903)
51 Cross-sectional studies/ (150828)
52 4 or 4 or 4 or 4 or 4 or 4 or 4 or 4 or 4 or 5 or 5 (1654583)
53 Meta-Analysis as Topic/ (12608)
54 meta analy$.tw. (43811)
55 metaanaly$.tw. (1130)
56 Meta-Analysis/ (37918)
57 (systematic adj (review$1 or overview$1)).tw. (35503)
58 exp Review Literature as Topic/ (6626)
59 or/53-58 (89518)
60 3 or 3 or 5 or 5 (2503667)
61 1 and 6 (2820)